time it is sobering to realize the absolute number of misadventures that actually do occur. However, it is to some degree reassuring to find that the percentage of potentially compensable events is quite small when one realizes that all diagnosis and treatment in medicine carry a greater or lesser risk. But perhaps the greatest significance of this study is that it addresses a social, economic and very human problem of medical care in an objective and scientific fashion—and this is indeed refreshing.

—MSMW

Prognostic Determinants in Chronic Hepatitis B Infection

A Reevaluation

RATIONALES for the diagnosis and therapy of patients with chronic hepatitis have improved in recent years as serologic markers have been discovered which permit identification of the infective virus,[1] and as attempts have been made to establish standard morphologic criteria in liver biopsy specimens which would predict prognosis.[2-4] Nevertheless, despite these advances, some patients with chronic hepatitis are not readily classifiable into clinical subgroups and are perplexing diagnostic and therapeutic challenges. Usually these "problem" patients are hepatitis B surface antigen (HB_sAg)-positive since hepatitis A is frequently self-limiting and does not result in cirrhosis,[5] while patients with HB_sAg-negative chronic hepatitis most often have recognizable histologic features which predict a favorable response to corticosteroid therapy. However, in some patients with chronic HB_sAg-positive infection, the morphologic determinants of prognosis seem less reliable, and there is growing uncertainty about the efficacy of corticosteroids.[6,7]

Elsewhere in this issue, a Specialty Conference is presented from the Hepatology Division and Department of Pathology of the John Wesley County Hospital, Los Angeles, which reviews a number of clinical, epidemiologic, pathologic and therapeutic aspects of chronic hepatitis B virus (HBV) infection. This center has had an extensive experience and their long-term observations have helped to delineate some special problems that occur with this form of hepatitis, and to direct attention to additional features of this disease which may be useful in judging prognosis and choice of therapy. What are some of these problems? What determinants of prognosis are most useful clinically in the HB_sAg-positive patient? First, the findings on liver biopsy, which are generally regarded as the cornerstone of diagnosis and management in patients with all types of chronic hepatitis, may occasionally be misleading in HBV infection. They are most useful in identifying chronic persistent or unresolved viral hepatitis which are benign and nonprogressive forms of chronic HBV infection. Liver biopsy findings also readily identify patients with bridging necrosis or an advanced cirrhosis, even though sampling error may prevent accurate assessment of its extent.[8] However, in many cases the morphologic features may be more difficult to interpret. Often focal areas of portal fibrosis or nodularity are seen although there is no generalized loss of architecture. Fibrous septae may bridge portal triads in some lobules but not in others and there may be an increase in inflammatory cell infiltrate and spotty or "piecemeal" periportal necrosis and fibrosis. Usually, however, central-portal bridging is absent. The process may wax and wane with time and even vary considerably in different areas of the same biopsy specimen.[9] Pathologists usually classify this example as chronic active hepatitis according to earlier international criteria,[10] which carried with them the clinical expectation that the chronic hepatitis would progress to a cirrhosis and that the process would be arrested with steroids. The recent experience of the John Wesley Hospital hepatologists and pathologists, as well as others, is that neither of these conclusions may necessarily be correct, particularly if the patient has chronic HB_sAg-positive hepatitis.

If the liver biopsy findings cannot always be relied upon to determine prognosis, are there other clinical findings that might be helpful in identifying those patients who are likely to progress to cirrhosis? Since a young asymptomatic male with chronic active hepatitis frequently has a relatively nonprogressive illness, the patient's age and sex and whether or not he has symptoms may be important. Age has long been recognized to influence the response to hepatitis infection, although the reasons have never been fully elucidated.[11] Changes in immune response to the HBV infection or relative impairments in the regenerative response have been offered as possible explanations. Dr. Peters has called this "the impaired regeneration syndrome" emphasizing that older

patients either die of progressive hepatic failure a few months after the onset of severe HB_sAg-positive hepatitis or eventually recover.[9]

However, most patients with advanced HB_sAg-positive cirrhosis (and this includes those patients with HB_sAg-positive disease associated with hepatocellular carcinoma) do not have any antecedent history of acute hepatitis. Anicteric viral hepatitis has long been recognized as a precursor of cirrhosis[12] and most patients with viral subacute hepatic necrosis in whom postnecrotic cirrhosis develops have had insidious onsets rather than typical acute hepatitis syndromes.[3] These differences in clinical presentations suggest that the immune response to HBV infection may be a critical determinant in the eventual outcome of the disease. Gudat and co-workers showed that there may be different fluorescent antibody patterns to HBV surface antigen and core antigen in liver cells in different clinical forms of HBV infection which may reflect a difference in the immune response.[13] They observed that patients with chronic active hepatitis have persistence of both core and surface antigen in hepatocytes bordering areas of cell necrosis and collapse, and that the persistence of core antigen near zones of collapse correlated with progressive disease in these patients (Bianchi, personal communication). Careful clinical-pathological correlations of this type may eventually determine whether fluorescent antibody studies of liver biopsy material will be helpful clinically.

Wedged hepatic vein pressure measurements (WHVP) and peritonoscopy are two other approaches that are being used by the Los Angeles group to help determine the extent and severity of the liver damage in HB_sAg-positive chronic active hepatitis. As illustrated by the case discussion, a progressive increase may be an early indication that cirrhosis is developing. Since elevations in WHVP are unusual in viral hepatitis this measurement may be useful.[14] However, further morphological and physiological correlations are needed, before WHVP can be accepted in routine clinical care. Peritonoscopy provides additional information about liver size and surface nodularity but may not necessarily accurately reflect hepatic functional mass. This technique, like WHVP, is invasive and requires a skillful operator with experience. A critical comparison of results of peritonoscopy with conventional diagnostic techniques is also needed before this potentially useful approach can be more widely accepted. There is also a need to develop noninvasive tests of liver function such as the ^{14}C-aminopyrine breath test which can accurately reflect changes in the mass of functioning hepatic tissue and which could be used to assess the natural history of chronic forms of liver disease, and their response to therapy.[15]

If these studies show that cirrhosis is developing in a patient with chronic HB_sAg-positive hepatitis, will corticosteroids benefit such patients? As Dr. Reynolds suggests, it may be several years before this question can be definitely answered although the Los Angeles group would probably vote no. However, caution must be exercised in interpreting the results of steroid therapy from different medical centers. Therefore the outcome of steroid trials in Los Angeles may differ from those in the Mayo Clinic or in London if the patient population is dissimilar. Could the poor response to steroids in Los Angeles reflect a difference in the natural history of disease since a large percentage of patients may have acquired HBV through drug abuse? Many are males and relatively asymptomatic and such patients are often unresponsive to steroid therapy. Experience elsewhere has been variable with older patients who are clinically ill, and who have more extensive histologic abnormalities including bridging necrosis or active cirrhosis. Some claim that steroids are effective but less frequently than when the HB_s antigen is negative.[16,17] A Mayo Clinic study suggests that HB_sAg-positive patients who are "e" antigen positive[18] may not respond to steroids, while those with antibody to "e" antigen do. A recent preliminary report suggests that circulating core antigen may be detected more frequently than "e" antigen and correlates more closely with deterioration and death than the presence of "e" antigen.[19]

Obviously more data are needed to more clearly define subpopulations of HB_sAg-positive patients with chronic active hepatitis before reaching a final judgment on the use of corticosteroid in this disease. No alternative treatment is immediately forthcoming, although trials with interferon and antiviral agents should and are receiving increased attention. Until then, corticosteroids should be used judiciously in HB_sAg-positive patients and reserved primarily for those with chronic active hepatitis who are over 40, are symptomatic, have biochemical evidence of significant activity and in whom liver biopsy findings show features consistent with progressive forms of chronic active hepatitis.[8] In view of the seriousness of potential

side effects, prolonged use of corticosteroids should be carefully avoided particularly if they do not elicit a clinical or biochemical response after several weeks of therapy. The problem is well illustrated by the patient in this month's specialty conference in whom cirrhosis and ascites developed despite a trial of corticosteroids.

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